

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization International Bureau



(43) International Publication Date
17 February 2005 (17.02.2005)

PCT

(10) International Publication Number
WO 2005/014041 A2

- (51) International Patent Classification⁷: A61K 39/39 (81) Designated States (*unless otherwise indicated, for every kind of national protection available*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SB, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.
- (21) International Application Number:
PCT/EP2004/008286
- (22) International Filing Date: 23 July 2004 (23.07.2004)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:
60/489,637 24 July 2003 (24.07.2003) US
- (71) Applicant (*for all designated States except AT, US*): NOVARTIS AG [CH/CH]; Lichtstrasse 35, CH-4056 Basel (CH).
- (71) Applicant (*for AT only*): NOVARTIS PHARMA GMBH [AT/AT]; Brunner Strasse 59, A-1230 Vienna (AT).
- (71) Applicant and
(72) Inventor: MATSUMOTO, Yoh [JP/JP]; Bessho 3-26-16, Minami-ku, Saitama 336-0021 (JP).
- (74) Agent: GRUBB, Phillip; Novartis AG, Corporate Intellectual Property, CH-4002 Basel (CH).
- (84) Designated States (*unless otherwise indicated, for every kind of regional protection available*): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

- *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.



WO 2005/014041 A2

(54) Title: MATERIALS AND METHODS FOR THE TREATMENT OF AMYLOID DISEASES

(57) Abstract: The present invention relates to methods for the treatment and prevention of neurological and vascular disorders related to beta-amyloid generation, in particular Alzheimer's Disease, Down's Syndrome, memory and cognitive impairment, dementia, amyloid neuropathies, brain inflammation, nerve and brain trauma, vascular amyloidosis, or cerebral haemorrhage with amyloidosis comprising administering an amyloid beta DNA vaccine, especially an amyloid beta DNA vaccine comprising cDNA coding for amyloid beta 1-42 or a fragment thereof; materials, such as pharmaceutical compositions, comprising said amyloid beta DNA vaccine, a process for the preparation of such amyloid beta DNA vaccine; and to methods for identifying an amyloid beta DNA vaccine suitable for the treatment and/or prevention of neurological and vascular disorders related to beta-amyloid generation.

Materials and Methods for the Treatment of Amyloid Diseases

The present invention relates to methods and materials for the treatment of diseases involving the abnormal accumulation of normally soluble proteins or peptides, in particular Alzheimer's Disease (AD), cerebrovascular amyloidosis, prion diseases and other degenerative diseases.

The pathology of Alzheimer's disease (AD) is characterized by the progressive deposition of the amyloid β -peptide ($A\beta$) in fibrillar form (see D.J. Selkoe, C.R. Abraham, Methods in Immunology, 388-404 (1986)).

Using a cDNA clone of the gene encoding amyloid beta protein as a genetic probe, it was shown that the gene is located on chromosome twenty-one and is expressed in many tissues of the body (D. Goldgaber et al, Science, 235, p. 777-780 (1987)). Quantitation of amyloid beta protein expression, as seen by its mRNA levels using the cDNA probe, has revealed that its level of expression in brain tissue of Alzheimer's patients was not above that seen for other tissues outside the central nervous system. Such a finding was of interest to researchers when noting that amyloid plaque formation only occurs in the brain (R. E. Tanzi et al, Science, 235, p. 880-884 (1987)).

US 5,753,624 describes a method for alleviating the symptoms of disease states associated with plaque formation such as AD or Parkinson's Disease comprising the step of administering to a patient in need thereof an effective amount of amyloid protein. The method described in US 5,753,624, generally comprises the administration of an adjuvant together with the vaccine.

Surprisingly, it has now been found that the number of plaques formed in the hippocampus and the cerebral cortex of rodents expressing human amyloid precursor protein (APP) can be reduced by vaccination of said rodents using an amyloid beta DNA vaccine. Hence, the present invention relates to a method for treatment and/or prevention of neurological and vascular disorders related to beta-amyloid generation comprising the step of administering to a warm-blooded animal, including a human patient, in need thereof an effective amount of an amyloid beta DNA vaccine.

After administration of A β DNA vaccines, corresponding A β peptide is produced at a relatively slow rate for a longer period of time compared with the A β peptide vaccination described in US 5,753,624 so that anti-A β antibodies, which are essential for reduction of the A β deposition in the brain, is also be raised gradually. In addition, DNA vaccination can be performed without use of any adjuvant. These advantages over A β peptide vaccination increase the main effects and reduce the side effects such as T cell-mediated autoimmune encephalomyelitis found in peptide vaccination. In accordance with the invention, there is provided a method to stimulate the appropriate metabolic regulatory systems (immune, CNS or endocrine) which retard the progress of the symptoms of neurological and vascular disorders related to beta-amyloid generation.

The term "neurological and vascular disorders related to beta-amyloid generation and/or aggregation" as used herein includes, but is not restricted to, neurodegenerative diseases like AD, Down's Syndrome, memory and cognitive impairment, dementia, amyloid neuropathies, brain inflammation, nerve and brain trauma, vascular amyloidosis, or cerebral haemorrhage with amyloidosis.

The method of the present invention can also be employed to treat other degenerative diseases where abnormally aggregated proteins play a role in the disease process, such as prion diseases (Creutzfeld-Jacobs, Gerstmann-Sträussler-Scheinker a.o.), Parkinsons disease or peripheral amyloidoses (TTR, SAA a.o.) by appropriate selection of the corresponding DNA sequences to create a DNA vaccine.

Additionally, the present invention provides amyloid beta DNA vaccines suitable to be used in the present invention. The term "amyloid beta DNA vaccine" as used herein relates to a vaccine comprising DNA coding for amyloid beta or a fragment thereof.

SHORT DESCRIPTION OF THE FIGURES

Figure 1 shows the number of amyloid plaques in the cerebral cortex of treated and untreated transgenic mice expressing human APP. The abbreviations used have the following meanings. No Tx denotes untreated animals; emp denotes animals treated with empty vector; A β denotes animals treated with A β vaccine, IgL denotes animals treated with IgL-A β vaccine, Fc denotes animals treated with the IgL-A β -Fc vaccine. The statistical

significance of the results is as follows: Fc vs. emp and no Tx, p<0.01; IgL vs emp and no Tx, p<0.01; A β vs. emp, NS; A β vs. p<0.05.

Figure 2 shows the numbers of positive pixels in the cerebral cortex of treated and untreated transgenic mice expressing human APP as determined from microphotographs using NIH image software. The abbreviations used have the meanings as for figure 1. The statistical significance of the results is as follows: Fc vs. emp and no Tx, p<0.01; IgL vs emp and no Tx, p<0.01; Ab vs emp and no Tx, p<0.01.

It can be shown by established test models that the use of an amyloid beta DNA vaccine results in the beneficial effects described herein. The person skilled in the pertinent art is fully enabled to select a relevant test model to prove such beneficial effects. The pharmaceutical activity of an amyloid beta DNA vaccine may, for example, be demonstrated in a clinical study or in a test procedure as essentially described hereinafter.

The therapeutic effect of amyloid beta DNA vaccines in the treatment and/or prevention of neurological and vascular disorders related to beta-amyloid generation can be confirmed, e.g., by clinical studies. Suitable clinical studies are, e.g., randomized, double-blind, placebo-controlled, parallel studies in patients with a history of AD. The disease status can be evaluated in AD patients using a battery of objective tests designed to measure cognitive ability. These include the mini-mental State Examination, the Verbal Fluency Task Examination (word name task and category task), evaluation on the Demattis Dementia Rating scale, and the Word-Association Task Examination of the Wechsler Memory Scale-Revised. The evaluation of the patients should preferably occur in regular time periods, e.g., every 4, 6 or 8 weeks.

The therapeutic effect of the amyloid beta DNA vaccine can result, e.g.,

- in an improved ability of the patient to answer questions, to place names with faces, and to complete sentences, to dress himself or to communicate,
- in an increased confidence of the patient in physical actions,
- in an increased score in the Mini-Mental State Exam,
- in improvement primarily in areas of attention and conceptualization, or
- in an improvement of the short term memory.

In one embodiment of the invention, the amyloid beta DNA vaccine consists of the cDNA coding for amyloid beta 1-42 or a fragment thereof and a suitable expression vector. In a preferred embodiment of the invention, the amyloid beta DNA vaccine comprises additionally a further DNA sequence coding for at least one unit selected from (a) a leader sequence increasing the efficacy of extracellular secretion of the translated peptide and (b) a peptide that stabilizes the produced protein such as Immunoglobulin Fc portion (see, e.g., P. S. Linsley et al, J Exp Med 1991, 173:721; A. Ashkenazi, et al, Proc. Natl. Acad. Sci. USA 1991, 88:10535). It could be confirmed in an *in vitro* assay that cells transfected with amyloid beta DNA vaccines possessing the leader sequence IgL added to the N terminus as disclosed herein release a certain amount of amyloid beta peptide to the culture medium.

Suitable expression vector include, but are not limited to, plasmids, eukaryotic vectors, and prokaryotic vectors, such as, for example, bacterial vectors.

Additionally, the present invention relates to a pharmaceutical composition suitable for enteral and parenteral administration to mammals (warm-blooded animals), including man, which comprises an amyloid beta DNA vaccine and optionally a pharmaceutically acceptable carrier. Typically, a pharmaceutical dosage unit of the present invention for the delivery of amyloid beta DNA vaccine in a low concentration comprises a liquid or solid carrier and an effective amount of amyloid beta DNA vaccine. The amyloid beta DNA vaccine is administered through standard methods, such as enteral, e.g. oral or rectal, and parenteral administration, including sublingual, intrathecal, subcutaneous and transdermal routes, and in dosage units that are either liquid or solid. The amyloid beta DNA vaccine may be administered with conventional excipients to permit ease of administration and accurate dosage delivery. In one embodiment of the invention, one or more of the active ingredients are administered intravenously.

The amyloid beta DNA vaccine can also be delivered by intrathecal injection (i.e. injection into the spinal fluid which bathes the brain and spinal chord tissue). Intrathecal injection of amyloid beta DNA vaccine into the spinal fluid can be performed as a bolus injection or via minipumps which can be implanted beneath the skin, providing a regular and constant delivery of amyloid beta DNA vaccine into the spinal fluid. Compositions and formulations for intrathecal administration may include sterile aqueous solutions which may also contain

buffers, diluents and other suitable additives such as, but not limited to, penetration enhancers, carrier compounds and other pharmaceutically acceptable carriers or excipients.

For testing the amyloid beta DNA vaccines in animal models, a solution of the vaccine or of an empty vector, e.g. at a dose of 100 µg, in phosphate-buffered saline (PBS), e.g. about 100 µl, can be injected intramuscularly at the anterior tibialis muscle. The vaccine can also be administered intradermally using a fine needle or a gene gun and intra-lymph node after making a small incision of the skin over the lymph node.

The pharmaceutical compositions according to the invention can be prepared in a manner known per se.

The effective dosage of amyloid beta DNA vaccine employed in human patients may vary depending on the particular amyloid beta DNA vaccine or pharmaceutical composition employed, the mode of administration, the condition being treated, the severity of the condition being treated. Thus, the dosage regimen of the amyloid beta DNA vaccine is selected in accordance with a variety of factors including the route of administration and the renal and hepatic function of the patient. A physician, clinician or veterinarian of ordinary skill can readily determine and prescribe the effective amount of the single active ingredients required to prevent, counter or arrest the progress of the condition treated. Optimal precision in achieving concentration of the active ingredients within the range that yields efficacy without toxicity requires a regimen based on the kinetics of the active ingredients' availability to target sites. This involves a consideration of the distribution, equilibrium, and elimination of the active ingredients. The dosage of the DNA vaccine to be applied to human patients is typically in the range of 10 to 5000 µg/injection.

Another aspect of the present invention relates to a method for identifying an amyloid beta DNA vaccine suitable for the treatment and/or prevention of neurological and vascular disorders related to beta-amyloid generation, the method comprising the steps of: a) vaccinating a rodent expressing amyloid precursor protein with a test amyloid beta DNA vaccine; and b) determining whether the test amyloid beta DNA vaccine reduces the number of plaques formed in the cerebral cortex or in the hippocampus. Rodents suitable for such methods are disclosed in EP 0 920 495 A.

In one embodiment, the invention provides a method for alleviating the symptoms of disease states associated with abnormal accumulation of and/or molecular organization of amyloid protein or amyloid plaques, which comprises administration of an effective amount of an active fragment of the amyloid beta DNA vaccine described herein to a patient in need thereof. Preferably, the DNA fragment codes for at least six amino acids.

The amyloid beta DNA vaccines used herein can be obtained, e.g., according to the methods described in the publications listed below, which are incorporated by reference into the present patent application:

- (a) Matsumoto, Y., Jee, Y. & Sugisaki, M. Successful TCR-based immunotherapy for autoimmune myocarditis with DNA vaccines after rapid identification of pathogenic TCR. *J. Immunol.* 164, 2248-2254 (2000);
- (b) A. Miyakoshi, W. K.Yoon, Y. Jee, Y. Matsumoto, Characterization of the antigen specificity and TCR repertoire and TCR-based DNA vaccine therapy in myelin basic protein-induced autoimmune encephalomyelitis in DA rats. *J. Immunol.* 170, 6371-6378 (2003).

This invention is further illustrated by the following examples which should not be construed as limiting. The contents of all references, patents and published patent applications cited throughout this application are hereby incorporated by reference.

EXAMPLES

Example 1: DNA Sequence listings

SEQ ID NO:1 - A β vaccine

CTCGAGACCATGGATGCAGAATTCC

1) 2)

GACATGACTCAGGATATGAAGTTCATCATCAAAATTGGTGTTCAGAAGATGTGG

GTTCAAACAAAGGTGCAATCATTGGACTCATGGTGGCGGTGTTGTCATAGCGTGAGGTACC

3) 4)

- 7 -

- 1) Xho I site
- 2) Kozak sequence/start
- 3) Stop codon
- 4) Kpn I site

SEQ ID NO:2 - IgL- $\text{A}\beta$ vaccine

GGATCCGCCACCATGGAGACAGACACACTCCTGCTAT

- 1)
- 2)

GGGTACTGCTGCTCTGGGTTCCAGGTTCCACTGGTGACGCGGCCCTCGAGGATGCAGAAT

- 3)

TCCGACATGACTCAGGATATGAAGTTCATCATCAAAATTGGTGTTCAGAAGATG

TGGGTTCAAACAAAGGTGCAATCATTGGACTCATGGTGGCGGTGTTGTCATAGCGTGAGGTAC

- C

- 4)

- 1) BamH I site
- 2) Kozak sequence/start of the Ig leader sequence
- 3) Xho I- $\text{A}\beta$ eta 1-42
- 4) Stop codon-Kpn I site

SEQ ID NO:3 - IgL- $\text{A}\beta$ -Fc vaccine

The Ig- $\text{A}\beta$ sequence (see above) was connected with the 801-1499 sequence of the Fc portion of human immunoglobulin heavy chain. The nucleotide sequence of this region is deposited in Gene Bank (Accession No. Y14737).

GGATCCGCCACCATGGAGACAGACACACTCCTGCTATGGGT

- 1)
- 2)

ACTGCTGCTCTGGGTTCCAGGTTCCACTGGTGACGCGGCCCTCGAGGATGCAGAATTCCG

ACATGACTCAGGATATGAAGTTCATCATCAAAATTGGTGTCTTGAGAAGATGTGGG

TTCAAACAAAGGTGCAATCATTGGACTCATGGTGGCGGTGTTGTCA TAGCGGGTACCGA

GCCCCAAATCT**TCT**GACAAAACCTCACACA**TCC**CCACCG**TCC**CCAGCACCTGAACCTCTGGG

GGGACCGTCAGTCTTCCCTTTCCCCCCC AAAACCC AAGGACACCCTCATGATCTCCGGAC

CCCTGAGGTACATGCGTGGTGGTGACGTGAGCCACGAAGACCCCTGAGGTCAAGTTCAA

CTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTA

CAACAGCACGTACCGTGGTCAGCGCCTCACCGTCCTGCACCAGGACTGGCTGAATGG

CAAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCCTCCCAGCCCCCATCGAGAAAAACCAT

CTCCAAAGCCAAAGGGCAGCCCCGAGAACCAACAGGTGTACACCCCTGCCCATCCCCGG

TGAGCTGACCAAGAACCGAGGTAGCCTGACCTGGTCAAAGGCTCTATCCCAGCGA

CATGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCCTCC

CGTGCTGGACTCCGACGGCTCCTTCTCCTACAGCAAGCTACCGTGGACAAGAGCAG

GTGGCAGCAGGGAACGTCTTCTATGCTCCGTATGCATGAGGCTCTGCACAACCACTA

CACGCAGAAGAGCCTCTCCCTGTCTCCGGTAAATGAGCGGCCGC

3) 4)

- 1) BamH I site
- 2) Kozak/start
- 3) stop codon
- 4) Not I site

Cystein residues in the original sequences (in the box) are substituted with serine.

All these sequences were inserted into a (non-viral) pTARGET Mammalian Expression Vector (Promega, Madison, WI, USA).

Example 2: Amyloid Beta DNA Vaccine Therapy against APP23 transgenic Mice

Amyloid Beta (A β) DNA vaccine therapy is started when transgenic (tg) APP23 mice are 4 months and 2 weeks old. Mice are divided into five groups (Group 1, IgL-A β -Fc Vax; Group 2, IgL-A β Vax; Group 3, A β Vax; Group 4, empty vector; Group 5, untreated; n=7 in each group), receive 13-14 vaccinations. Three different A β vaccines and an empty vector at a dose of 100 μ g in 100 μ l phosphate-buffered saline (PBS) are injected intramuscularly at the anterior tibialis muscle. The animals are sacrificed when 9 months old. Cerebra are removed and cut sagitally into 4 slices for paraffin and frozen sections and biochemistry.

Immunohistochemical staining with anti-A β (6F/3D) (6F/3D; Dako, Tokyo, Japan) and horse-radish peroxidase (HRP)-labeled VECTSTAIN Elite ABC Kit (Vector, Burlingame, CA) is performed using 6 μ m paraffin-embedded sections. Sections are pretreated with formic acid for 3 min. Quantitative analysis is performed by counting amyloid plaques in the cortex of treated and untreated tg mice. In addition, microphotographs including plaques (5-7 fields) are taken and analyzed using a NIH image software (a free software provided by US National Institute for Health) to estimate the size of the plaques and extent of small granular deposition.

Anti-A β antibodies in the sera of Tg mice are measured by anti-A β ELISA. ELISA plates are coated with A β 1-40 peptide (Peptide Institute, Inc., Osaka, Japan) and the titer of the antibodies are detected using biotin-anti mouse IgG (Vector) and the ABC complex. The antibody titer is defined as the reciprocal of the greatest dilution of sera that gives half-maximal binding to A β that is determined by dividing the highest OD₄₅₀ value in the dilution range of each sample by 2.

Counting the number of plaques in the cerebral cortex of treated and untreated tg mice shows that the plaques decreased significantly in number (Fig. 1). Fc vaccine shows the most significant effect whereas A β vaccine reduces fewer plaques.

In order to estimate the size of plaques and the presence or absence of granular A β deposition in the cortex, 5-7 fields including one or more plaques or granular deposition are selected and microphotographs are taken. These images are analyzed using the NIH image software (Fig. 2). The number of positive pixels is markedly reduced in the treated group (Fc, IgL and A β). This finding indicates that DNA vaccination suppresses granular A β deposition more effectively than plaque formation. For instance, A β vaccine suppresses plaque formation less effectively but the level of positive pixels is almost the same as that of Fc vaccine which is most effective for suppression of plaque formation (Fig. 1). These findings suggest that A β DNA vaccination inhibit A β granular deposition principally and thereby reduce the number and size of plaques.

In the hippocampus, still a small number of plaques can be observed in the control groups at this stage. In the treated groups no plaque can be found in this region.

The above findings demonstrate that A β DNA vaccination can be a therapeutic tool for the treatment and prevention of human Alzheimer's disease.

What is claimed is:

1. A method for the treatment of neurological and vascular disorders related to beta-amyloid generation comprising the step of administering to a warm-blooded animal in need thereof an effective amount of an amyloid beta DNA vaccine.
2. A method for the prevention of neurological and vascular disorders related to beta-amyloid generation comprising the step of administering to a warm-blooded animal in need thereof an effective amount of an amyloid beta DNA vaccine.
3. The method according to claim 1 or 2 wherein the warm-blooded animal is a human.
4. The use of an amyloid beta DNA vaccine for the preparation of a medicament for the treatment or prevention of disease states associated with beta-amyloid generation.
5. The method of claim 1, 2 or 3 wherein the disorder is selected from the group consisting of Alzheimer's Disease, Down's Syndrome, memory and cognitive impairment, dementia, amyloid neuropathies, brain inflammation, nerve and brain trauma, vascular amyloidosis, or cerebral haemorrhage with amyloidosis.
6. The method of claim 5 wherein the disorder is Alzheimer's Disease.
7. The method of claim 1, 2 or 3 wherein the disorder is selected from the group consisting of prion diseases, Parkinsons Disease and peripheral amyloidoses.
8. An amyloid beta DNA vaccine comprising cDNA coding for amyloid beta 1-42 or a fragment thereof.
9. The amyloid beta DNA vaccine of claim 8 wherein the cDNA coding for amyloid beta 1-42 or a fragment thereof is placed in a suitable expression vector.
10. An amyloid beta DNA vaccine consisting of cDNA coding for amyloid beta 1-42 or a fragment thereof and a suitable expression vector.

11. The amyloid beta DNA vaccine according to any one of claims 8 to 10 comprising additionally a further DNA sequence coding for at least one unit selected from (a) a leader sequence increasing the efficacy of extracellular secretion of the translated peptide and (b) a peptide that stabilizes the produced protein.
12. A method for the treatment of neurological and vascular disorders related to beta-amyloid generation comprising the step of administering to a warm-blooded animal in need thereof an effective amount of an amyloid beta DNA vaccine according to any one of claims 8 to 11.
13. A method for the prevention of neurological and vascular disorders related to beta-amyloid generation comprising the step of administering to a warm-blooded animal in need thereof an effective amount of an amyloid beta DNA vaccine according to any one of claims 8 to 11.
14. The method according to claim 12 or 13 wherein the warm-blooded animal is a human.
15. A pharmaceutical composition which comprises an amyloid beta DNA vaccine according to any one of claims 8 to 11 and a pharmaceutically acceptable carrier.
16. A pharmaceutical composition for the treatment and/or prevention of neurological and vascular disorders related to beta-amyloid generation which comprises an amyloid beta DNA vaccine according to any one of claims 8 to 11 in an amount effective to alleviate one or more symptoms of said disease state and a pharmaceutically acceptable carrier.
17. Process for the preparation of an amyloid beta DNA vaccine including the steps of incorporating the amyloid beta DNA vaccine into a suitable expression vector.
18. A method for identifying an amyloid beta DNA vaccine suitable for the treatment and/or prevention of neurological and vascular disorders related to beta-amyloid generation, the method comprising the steps of: a) vaccinating a rodent expressing human amyloid precursor protein with a test amyloid beta DNA vaccine; and b) determining whether the test amyloid beta DNA vaccine reduces the number of plaques formed in the cerebral cortex.

19. A method for identifying an amyloid beta DNA vaccine suitable for the treatment and/or prevention of neurological and vascular disorders related to beta-amyloid generation, the method comprising the steps of: a) vaccinating a rodent expressing human amyloid precursor protein with a test amyloid beta DNA vaccine; and b) determining whether the test amyloid beta DNA vaccine reduces the number of plaques formed in the hippocampus.

Fig. 1

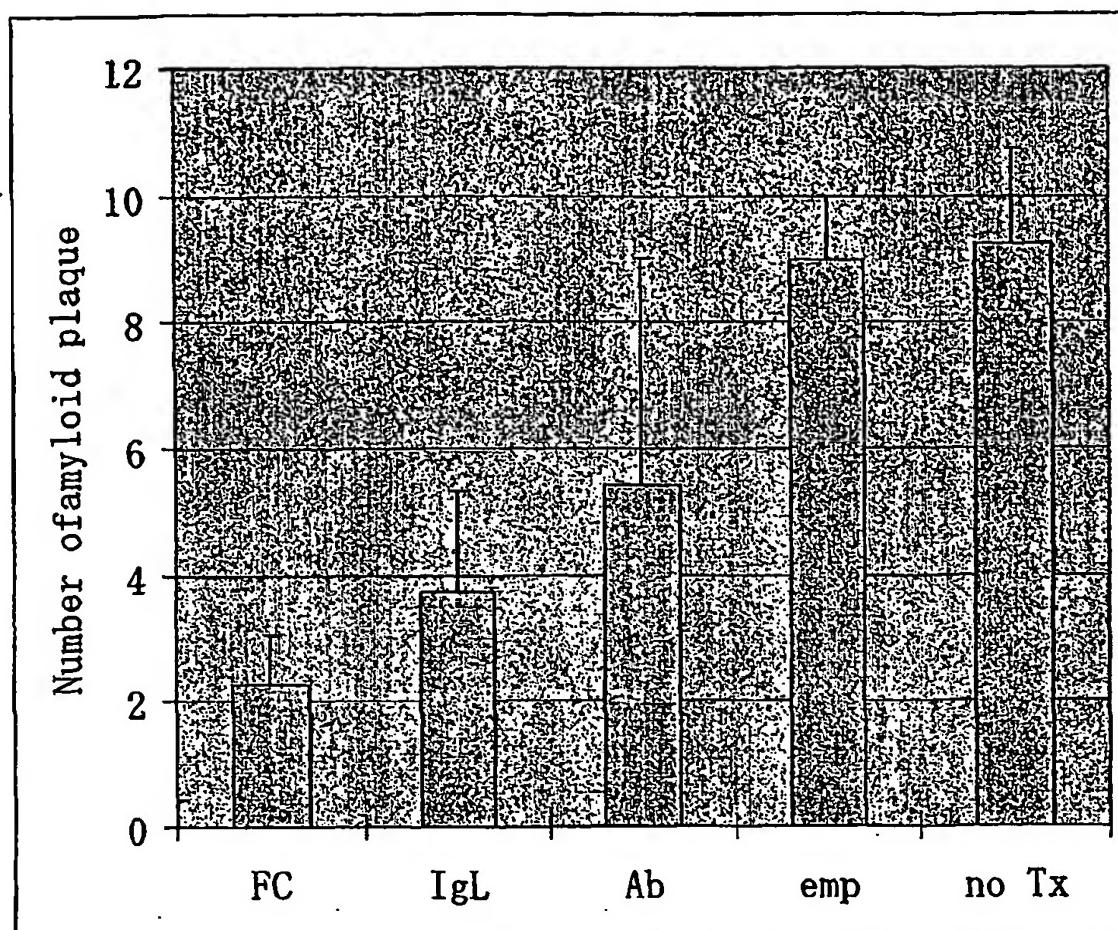


Fig. 2

